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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/368,989	08/05/1999	FRED J. STEVENS	0003/00332	6185

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CHERSKOV AND FLAYNIK
C/O MICHAEL J CHERSKOV
THE CIVIC OPERA BUILDING SUITE 1447
20 NORTH WACKER DRIVE
CHICAGO, IL 60606

EXAMINER	
COOK, LISA V	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 04/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/368,989	STEVENS ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,12-14 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,12-14 and 21* is/are rejected.

7)☒ Claim(s) *20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Compliant Amendment

1. Applicant's amendment filed December 15, 2004 is not in compliance. Claim 12 is identified with the status (previously amended). However only 7 status identifiers are permissible. The appropriate claim status identifier should be ***(previously presented)***. Appropriate correction is required.

Claim Status

2. Claims 10, 12-14 and 21 are currently pending and under consideration.

3. Objections and/or rejections of record not reiterated below have been withdrawn.

OBJECTIONS WITHDRAWN

Information Disclosure Statement

4. Applicants have addressed the remarks noted by the examiner regarding the IDS, therein obviating the objection. Accordingly the objection is withdrawn.

NEW GROUNDS OF REJECTION NECESSITATED BY AMENDMENT

Claim Objections

5. Claim 10 Claim is objected to because of the following informalities: In line 2 "molecular" is misspelled. It should be "**molecule**". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 10, 12-14 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 10 is vague and indefinite because it is not clear what the composition comprises. For example, claim 10 recites antigen binding sites as well as antigen binding regions. It is not clear if these are separate regions or the same binding areas. Also the molecule "comprises" two antigen-binding sites and two complementary segments while further "consisting of" linked first and second moieties. It is not clear if the molecule only contains the first and second moieties or other compositions. Appropriate correction is required to clarify the claim.

B. Claim 10 is vague and indefinite in reciting that the first moiety and the second moiety are rotated about 180 degrees from the other because it is not clear if the moieties are in a straight line (180 degrees) or at some other rotated configuration (90 degrees). The limitation is not defined by the claims or the specification. Therefore the metes and bounds of the claim cannot be determined and one of ordinary skill would not be reasonably appraised of the scope of the invention. In order to obviate this rejection the wording "rotated about" should be eliminated from the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 10, 12-14 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In particular, claim 10 is drawn to an isolated molecule containing two antigen binding sites and complementary determining segments positioned at opposite ends of the molecule wherein the antigen binding regions are linked to non-binding regions via a peptide linker whereby the moieties are light chain variable domains.

However the mere description of such compositions without the structures (via SEQ ID NO) does not provide possession of the claimed invention. The claims and specification fail to provide the identity or structure of this isolated molecule. The specification does not provide evidence of a sequence identification number meeting/having the descriptive identification. The specification at page 10 lines 9-29 discloses that the structure initially start with known constructs identified in the prior art but were modified to form applicants "Janusbodies". Although the starting materials are found in the prior art, this does not provide adequate description of the final modified constructs. The specification does not state the identity by sequence or any structural characteristics of any other sequence that has the claimed "Janusbodies" characteristics.

Moreover, there is evidence that other sequences have not yet been identified (see specification page 5 lines 6-8) therefore; applicants' vague description of an isolated molecule has not been adequately described.

In view of the lack of evidence, it is apparent that Applicants were not in possession of sequences having the described isolated molecule compositions of claim 10, at the time of filing the instant application. The skilled artisan cannot envision the detailed structure of the isolated molecular sequence, thus conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

An adequate description requires more than a mere statement that it is part of the invention. The structure is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. The protein activity characteristics and domain requirements distinguish the protein only by what it does, i.e., protein activity, which are purely functional distinctions. Even where there is an actual reduction to practice, which may demonstrate possession of an embodiment of an invention, it does not necessarily describe what the claimed invention is. The instant specification and claims describe an isolated molecule by its protein function (light variable binding domains), however this description does not describe the claimed isolated molecule itself.

See also, *In The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), where the court held that a generic statement that defines a genus of amino acids/nucleic acids by only their functional activity does not provide an adequate description of the genus.

The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of protein/DNA molecules, usually defined by an amino acid sequence or a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". Thus a skilled artisan cannot envision all the contemplated protein/nucleotide sequences by the detailed chemical structure of the claimed polynucleotides and therefore conception cannot be achieved until reduction to practice has occurred.

Thus, in the absence of sequence information of the amino acid, an isolated molecule described only by its protein activity fails to meet the written description requirements. Therefore the full breadth of the claims, have not meet the required written description provision of 35 USC 112, first paragraph.

Response to Arguments

Applicant contends that the canceling of claims 25-31 which recited specific light chain variable domains has obviated the rejection (of record in paper #25 on page 7 paragraph 14). This argument was carefully considered but not found persuasive because claims 10, 12-14 and 21 were also included in the rejection but were not addressed in the arguments. Accordingly the rejection is maintained.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102((e), f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 10, 12-13 and 21 are rejected under 35 U.S.C. 103(b) as being unpatentable over Davis et al. (WO 97/14719) or Davis et al. (WO 97/38102) in view of Stevens et al. (Proc. Natl. Acad. Sci. USA, Vol77, No.2, pages 1144-1148, 2/1980 Immunology).

Davis et al. (WO 97/14719) disclose molecules with linked variable light chains. The multivalent/ multi-specific antigen binding proteins consist of multiple variable domains - V_L (antibody light chains) with antigen binding sites (A, B, etc). See abstract and pages 8-9.

This reads on applicants' first moiety and second moiety joined by a peptide linker (V_LA-linker -V_LB). See figures 33-35, 43 and claims 2, 6, 7. With respect to the light chain variable rotated about 180 degrees it is noted that the references teaches this because the V_L moieties are in a straight line opposite each other in the molecule. See figure 35 for example.

The molecules also comprise a complementary determining segments (CDRs) and variable heavy chain regions. The light chains are identical (from the same gene). See page 1 lines 10-24. The antigen binding sites can be the same (identical). See page 9 lines 4-6.

Davis et al. (WO 97/38102) also discloses multivalent and multispecific antigen binding proteins. See page 1 lines 14-31. In this reference the variable light chains are linked together to form multiple binding domains. See page 22 lines 30-34, for example. Also pages 18-19 and figures 20-22.

Davis et al. (WO 9714719) and Davis et al. (WO 97/38102) differ from the instant invention in not specifically teaching the utility of a hydrophobic residue between the first and second moieties.

However, Stevens et al. teach light chain association characteristics. Stevens et al. further teach that the association (binding) of light chains is enhanced when a hydrophobic residue is present in the molecule. The hydrophobic residue facilitates dimerization and variable chain association. See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include a hydrophobic residue as taught by Stevens et al. in the moiety constructions of Davis et al. (WO 9714719) and Davis et al. (WO 97/38102) because Stevens et al. taught that that the association (binding) of moieties, such as dimers and variable chains is enhanced when a hydrophobic residue is present in the molecule. See abstract.

One of ordinary skill would have been motivated to incorporate the hydrophobic residue in order to produce stable compositions.

II. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (WO 97/14719) or Davis et al. (WO 97/38102) in view of Stevens et al. (Proc. Natl. Acad. Sci. USA, Vol77, No.2, pages 1144-1148, 2/1980 Immunology) as applied to claims 10, 12–13, and 21 above, and further in view of Goding (Journal of Immunology, 1980, 124(5), pages 2082-2088)-Abstract Only and Skoog et al. (Scand. J. Immunolgy, 1980, 11(4), pages 369-376)-Abstract Only.

Please see Davis et al. (WO 97/14719) or Davis et al. (WO 97/38102) in view of Stevens et al. (Proc. Natl. Acad. Sci. USA, Vol77, No.2, pages 1144-1148, 2/1980 Immunology) as set forth above.

Davis et al. (WO 97/14719) or Davis et al. (WO 97/38102) in view of Stevens et al. (Proc. Natl. Acad. Sci. USA, Vol77, No.2, pages 1144-1148, 2/1980 Immunology) differ from the instant invention in not specifically reciting the weight requirements of claim 14. (between 20,000 and 30,000 daltons).

However, both references of Goding and Skoog et al. teach antigen-binding molecules weighing between 20,000 to 30,000 daltons. See IgD moiety cleaved C-terminal weighing 20,000 daltons in Goding et al. and the glycoprotein moieties weighing 30,000 daltons which bind ALG in Skoog et al.

Therefore, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to utilize a molecule weighing between 20,000 and 30,000 daltons as taught by Goding and Skoog et al. in the moiety constructs of Davis et al. (WO 97/14719) or Davis et al. (WO 97/38102) in view of Stevens et al. (Proc. Natl. Acad. Sci. USA, Vol77, No.2, pages 1144-1148, 2/1980 Immunology) to produce a dimeric antigen binding molecule because Goding and Skooog et al. taught that moieties weighing between 20,000 to 30,000 daltons retained binding affinity for antigens. See abstract.

A person of ordinary skill in the art would have had a reasonable expectation of success utilizing such compounds, because the recited weight ranges were previously demonstrated. One of ordinary skill in the art would have been motivated to do use small moieties (antibody fragments between 20,000 to 30,000 daltons) in order to eliminate the use of large moieties, which can be cumbersome with slow clearance rates.

Response to Arguments

Applicants contend that the references of Stevens et al. in view of Berry et al. did not make obvious the instant invention because the newly recited limitations regarding the 180degree positioning of the first and second moiety as well as the intermediate positioning of the hydrophobic residue were not disclosed.

This argument was carefully considered and found persuasive. Therefore the references of Davis et al. (WO 97/14719) or Davis et al. (WO 97/38102) in view of Stevens et al. (Proc. Natl. Acad. Sci. USA, Vol77, No.2, pages 1144-1148, 2/1980 Immunology) has been cited to make the claimed invention obvious.

With respect to claim 14, Applicant argues that the primary references of Stevens and Berry were deficient therefore the rejection including Goding and Skoog et al. were deficient. This argument was carefully considered and found persuasive. A new rejection has been made over Davis et al. (WO 97/14719) or Davis et al. (WO 97/38102) in view of Stevens et al. (Proc. Natl. Acad. Sci. USA, Vol77, No.2, pages 1144-1148, 2/1980 Immunology) to make obvious the opposite positioning of the antigen receptors (see WO 97/14719 - figures 33-35, 43 and claims 2, 6, 7; see WO 97/38102 - pages 18-19 and figures 20-22) and the inclusion of a hydrophobic residue (see Stevens et al. –abstract).

9. For reasons aforementioned and already of record, no claims are allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action.

In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to Group TC 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JEFFREY S. PARKIN, PH.D.
PRIMARY EXAMINER

Lisa V. Cook 4/4/05

Lisa V. Cook
Patent Examiner
Art Unit: 1641
Remsen 3C-70
571-272-0816
3/22/05